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Designing vaccines for developing-country populations: ideal attributes, delivery devices, and presentation formats

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Abstract

This article discusses the importance of designing vaccine products with attributes that will help to mitigate challenges that immunization programs are facing as they introduce new vaccines. The handling, management, and use of vaccines is becoming increasingly complex; placing an increased burden on health care professionals who distribute and deliver vaccines and on supply systems that need to transport, manage, store, and track disparate products. Now is the time to influence future vaccine products to mitigate the complexity and pave the way for success.

Keywords: *Cold chain; Product profile; Vaccine Presentation and Packaging Advisory Group*

1. Vaccine products: what will the future bring?

The future for vaccines is bright as new vaccines wield the ability to avert additional diseases; new delivery, formulation, and stabilization methods improve immunization effectiveness; and new sources of funding are secured to ensure that those in greatest need have access to these life-saving products [1-4]. Progress in these areas should provide health benefits to all and financial benefits to communities and to industry.

There are some practical, logistical, and safety concerns that accompany the many changes that developing-country immunization programs are already experiencing as new vaccine products are being introduced. Few programs have the cold chain storage capacity to handle increasing volumes [5-7]. Many new vaccines will be targeted to different age groups than the traditional course of vaccines for infants and require new delivery strategies. For example, human papillomavirus (HPV) vaccine is provided to adolescent girls and is often given in schools [8]. In addition,

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new product handling instructions continue to emerge. For example, the World Health Organization's (WHO) multi-dose vial policy is being updated to incorporate new product formats such as low-dose liquid vaccines without preservatives [9,10]. Changes to vaccine storage recommendations are also envisioned to allow for controlled ambient temperature storage to facilitate timely vaccination of populations living beyond the reach of the existing cold chain infrastructure (e.g., delivery of a dose of hepatitis B vaccine at birth), for rapid response to pandemics, and to free up cold chain space for less-heat-stable vaccines [4,11,12]. As we project forward a decade or two, we can also predict that new vaccine-delivery methods such as jet injectors, micro-needle patches, dissolvable tablets, sublingual gels, and nasal drops or sprays will become more available [13,14].

The bottom line is that in the future the handling, management, and use of vaccines will become increasingly complex. This will place an increased burden on health care professionals who distribute and deliver vaccines and on supply systems that need to transport, manage, store, and track disparate products. The potential for human error may also increase and could result in negative health outcomes for vaccine recipients if products are stored, measured, reconstituted, or delivered incorrectly. Now is the time to influence future vaccine products to mitigate the complexity and pave the way for success. Steps are already being taken in this direction.

2. A generic preferred product profile for vaccines

The Vaccine Presentation and Packaging Advisory Group (VPPAG) is working to provide practical guidance to vaccine manufacturers to help ensure that the public-sector market in developing countries is able to implement rapid and effective uptake of essential, new vaccines. The VPPAG was originally formed by the GAVI Alliance secretariat to address product profile issues for pneumococcal and rotavirus vaccines and has now been reinstated under the WHO. The group provides a unique forum for industry and public-sector dialogue on presentation and packaging of vaccine products. VPPAG membership includes representatives from the International Federation of Pharmaceutical Manufacturers' Association; the Developing Country Vaccine Manufacturers' Network; WHO's Department of Immunization, Vaccines, and Biologicals (both the Expanded Programme on Immunization and Quality, Safety, and Standards teams); PATH; the United Nations Children's Fund (UNICEF) Supply and Program Divisions; John Snow, Inc.; the United States Centers for Disease Control and Prevention (CDC); and the GAVI Alliance secretariat.

The VPPAG recently completed a draft generic preferred product profile for new vaccines for developing countries. This consensus document between industry and the public sector is meant to serve as a resource for any entity involved in research and development of vaccines for developing-country markets.

An overview of existing VPPAG generic recommendations for vaccines in development and the VPPAG's ongoing work program in this area is provided below (**Table 1**). The complete document is available at *http://sites.google.com/site/vppagp/gppp* [15].

3. Roles for vaccine developers

The generic recommendations above and in **Table 1** are meant to provide signals to vaccine developers about the preferences and concerns of the public-sector, developing-country markets. These include preferences for products with smaller overall volumes, products and packaging made of materials that minimize environmental impact, products that are intuitively easy to prepare and administer, and product formats that minimize the possibility for human error. Many of these attributes are likely also important for other, more lucrative markets. Private physicians' offices in industrialized countries often use small, domestic refrigerators to store vaccines and therefore experience cold chain capacity issues [16]. Nurses and pharmacists in the United States and Europe will also be impacted by the increasing number of vaccines and complexity of product formats and delivery routes. If a vaccine product can be created that will serve both markets, efficiencies of scale can be achieved that should benefit all.

Table 1. Existing VPPAG generic recommendations for new vaccines and VPPAG work program (Version 2.1, dated 10 August 2009)

Parameter	Recommendations for producers and developers	VPPAG work program to develop additional recommendations
Formulation		
Single- vs. multi-component vaccines	Provide vaccines, whenever possible, in "ready-to-use" presentations that do not require the mixing of components.	
Heat stability	• Vaccines should be stable at standard cold chain temperatures (2° to 8 °C). • Maximize vaccine heat stability to improve effectiveness and enable higher temperature storage. • Label/license products for higher temperature storage, whenever possible.	1.1 Monitor and contribute to ongoing work to define the desirable higher temperature storage conditions for vaccines and add specificity to recommendations, as further evidence becomes available. 1.2 Contribute to ongoing work to develop policy and guidelines for potential higher temperature storage of vaccines.
Freeze stability	Formulate vaccines so that they will not be damaged by freezing, where feasible.	
Antimicrobial preservatives	Include preservative in multi-dose vials of injectable vaccines, where feasible, to allow safe use of opened containers in subsequent sessions.	
Product format	Provide vaccines in formats to minimize 1) number of steps and 2) potential for error during preparation and administration.	
Optimal number of doses per primary container		2.1 Obtain and assess data and tools to determine if generic guidelines can be made with regard to optimal number of doses per container for new vaccines. 2.2. Explore the need to define parameters for vaccines that must be used within a "short time frame" of preparation.
Prefilled injection devices	Vaccines in prefilled injection devices should have both space-saving and autodisabling features.	3.1 Assess country demand and willingness to pay for compact, prefilled autodisable devices (CPADs) for specific vaccines. 3.2 Assess non-cost obstacles for use of CPADs. 3.3 Identify solutions to minimize storage space required.

Parameter	Recommendations for producers and developers	VPPAG work program to develop additional recommendations
Labeling		
Product labeling and package insert		4.1 Assess potential improvements and innovations for product labeling and package inserts that could improve immunization safety and efficiency. 4.2 Develop guidance on the optimal location and number of inserts in secondary or tertiary packaging that will meet regulatory requirements.
Vaccine vial monitors (VVMs)	Include VVMs on all vaccines, as recommended by WHO and UNICEF.	
Freeze indicators		5.1 Explore new options for prevention and/or detection of freeze damage, including licensing of some vaccines for storage at higher temperatures and use of freeze indicators on primary containers and/or packaging.
Visual cue regarding discard		6.1 Work with the WHO and industry to explore the concept of placing a visual cue on primary containers of vaccine to identify which vials may or may not be kept for subsequent sessions.
Packaging		
Multi-component vaccines		7.1 Assess the programmatic impact of the vial clip and other mechanisms for keeping vaccine components together. 7.2 Develop recommendations on keeping vaccine components together during all or part of vaccine distribution and storage.
Maximum packed volume	Minimize volume and weight of secondary and tertiary packaging, as well as the need for repackaging for in-country supply chain distribution.	8.1 Update existing WHO maximum packed volume recommendations and provide generic maximum packed volumes for different vaccine types and containers (e.g., liquid in vial, lyophilized in vial with diluent, liquid in CPAD, oral in dropper, etc.) in secondary packaging and grossing factors for tertiary packaging.
Materials, including the primary container and delivery device	1. **Use materials for delivery devices, primary containers, and secondary and tertiary packaging that minimize the environmental impact of waste disposal for resource-limited systems.**	8.2 Consult with industry on feasible recommendations for packaging materials as well as maximum volume recommendations for primary containers and secondary and tertiary packaging for different vaccine types and containers, and advise the WHO on setting these as recommendations for prequalified vaccines.

The key differences between the industrialized and developing-country markets for vaccines are the latter's lesser resources to pay for the products themselves and for the storage, distribution, personnel, and training to properly handle and administer them. While the generic recommendations provide a good sense of direction, they can only go so far in assisting vaccine developers. There are also product-specific considerations that need to be taken into account such as the deployment strategy (e.g., campaign versus outreach settings) and the innate characteristics of the vaccine (e.g., maximum achievable stability and production method). These considerations will impact the ideal product profile for the vaccine. For example, a vaccine used mostly in campaign settings may be more cost-effective in a multi-dose primary container, and a vaccine that must be freeze-dried to achieve adequate stability may need to be physically bundled with its diluent to prevent reconstitution errors. Vaccine-specific analyses of these issues will be required. The VPPAG can serve as resource to help gather and analyze these data and work through issues together with industry and the public sector to reach consensus on the best product profile for a specific vaccine for developing-country markets.

At present, the VPPAG is gathering data to inform a product profile for second-generation HPV vaccines. The work includes review of qualitative and quantitative data from immunization programs that have recently introduced first generation versions of HPV vaccine, temperature monitoring studies to explore the possibility of controlled ambient temperature storage of HPV vaccine during the last stage of distribution (e.g., from health centers to schools), and discussions with vaccine producers about potential new containers and temperature storage requirements for the vaccine.

Work on other specific product profiles will likely follow, and industry is encouraged to initiate dialogue with the VPPAG on specific issues and products, as helpful.

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REFERENCES

1. **World Health Organization** (WHO), The United Nations Children's Fund, World Bank. 2009. State of the World's Vaccines and Immunization. 3rd ed. Geneva: WHO.
2. **Weniger, B.G., M.J. Papania**. 2008. Alternative vaccine delivery methods. [Chapter 61] In: Plotkin, S.A., W.A. Orenstein, and P.A. Offit. Vaccines. 5th ed. Philadelphia, PA: Saunders (Elsevier); 1357-1392.
3. **Levine, M.M., and R. Robins-Browne**. 2009. Vaccines, global health and social equity. Immunol Cell Biol. 87:274-8.
4. **Chen, D., and Kristensen, D**. 2009. Opportunities and challenges of developing thermostable vaccines. Expert Rev. Vaccines. 8:547-557.
5. **WHO**. 2009. Workgroup 5. Cold Chain and Logistics Systems for Preparedness for the Introduction of PCV, Rotavirus, HPV and Other New Vaccines. Geneva: WHO. [Online] http://www.who.int/nuvi/NUVI_MeetingReport.pdf [7 Jan 2009, last date accessed.]
6. **PATH**. 2009. Optimizing Vaccine Supply Chains. Seattle: PATH. [Online] http://www.who.int/immunization_delivery/systems_policy/Optimize_ urgency _EN_2009.pdf [7 Jan 2009, last date accessed.]
7. **Parmar, D., E.M. Baruwa, P. Zuber, and S. Kone**. 2010. Impact of wastage on single and multi-dose vaccine vials: Implications for introducing pneumococcal vaccines in developing countries. Hum Vaccin. 6:[Epub ahead of print].
8. **Wong, L.P**. 2009. HPV information needs, educational messages and channel of delivery preferences: views from developing country with multiethnic populations. Vaccine. 27:1410-5.
9. **WHO**. 2000. WHO Policy Statement: The Use of Opened Multi-dose Vials of Vaccine in Subsequent Immunization Sessions. Geneva: WHO. [Online] http://www.who.int/vaccines-documents/DocsPDF99/www9924.pdf [7 Jan 2010, last date accessed.]
10. **WHO**. 2008. Technologies and Logistics Advisory Committee (TLAC): Meeting Report 3-4 September 2008. Geneva, Switzerland. [Online] http://www.who.int/immunization_delivery/TLAC-report_2008-09.pdf [7 Jan 2010, last date accessed.]
11. **Schöndorf, I., A. Banzhoff, U. Nicolay, and F. Diaz Mitoma**. 2007. Overcoming the need for a cold chain with conjugated meningococcal Group C vaccine. Vaccine. 25:1175-1182.
12. **PATH, WHO**. 2009. Increasing the acceptable temperature range for certain vaccines. Optimize e-newsletter. 3. [Online] http://www.who.int/immunization_delivery/systems_policy/optimize_newsletter_nov_02nov09.pdf [7 Jan 2009, last date accessed.]
13. **Simerska, P., P.M. Moyle, C. Olive, and I. Toth.** 2009. Oral vaccine delivery—new strategies and technologies. Curr Drug Deliv. 6:347-58.
14. **Prausnitz, M.R., J.A. Mikszta, M. Cormier, and A.K. Andrianov**. 2009. Microneedle-based vaccines. Curr Top Microbiol Immunol. 333:369-93.
15. **Vaccine Presentation and Packaging Advisory Group**. 2009. Generic Preferred Product Profile for Vaccines. Version 2.1. [Online] http://sites.google.com/site/vppagp/gppp [7 Jan 2010, last date accessed.]
16. **Baker, D.J., J. Jerram, and L.A. Reid**. 2002. Failure of the vaccine cold chain following modification of a domestic refrigerator. J New Zealand Medical Assoc. 115:U251. [Online] http://www.nzmj.com/journal/115-1165/251/ [7 Jan 2009, last date accessed.]